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The Phakomatoses: Dermatologic Clues to Neurologic Anomalies

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The phakomatoses of particular interest to neurologists including Sturge-Weber syndrome, neurofibromatosis type 1, neurofibromatosis type 2, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome are presented. The physical manifestations required for clinical diagnosis, the neurologic features, and recommendations for management are given. The molecular etiology and genetic aspects of these disorders are briefly discussed as well as future implications of on-going research.
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There is an oft-quoted dysmorphologic maxim, "The face reflects the . . . brain"[1] indicating that anomalies of facial development are frequently associated with brain malformation. Similarly, there are a variety of dermatologic findings that signal potential neurologic sequelae. The term phakomatoses is an old one which is applied to a diverse group of disorders depending on one's definition. Van der Hoeve first coined the term in 1932 because of the lens-like retinal tumors (phakomata) seen in several of these disorders.[2] Others, citing the Greek root phakos, meaning "mother spot"[3] or birthmark, apply the term to disorders of abnormal tissue growth or tumor formation occurring in conjunction with birthmarks. This review will describe several distinct disorders with involvement of both the skin and central nervous system tissues. Several classic phakomatoses will not be discussed: specifically, tuberous sclerosis complex (TSC) is not included because it has recently been thoroughly reviewed in this journal[4] and von Hippel Lindau is not included because cutaneous findings are not a defining feature.

Sturge-Weber Syndrome

Capillary malformation or port wine stain (PWS) is the most common congenital vascular malformation being found in 0.3% of newborns,[5] and, when it occurs on the face, it greatly worries parents because of its cosmetic implications. The astute physician, however, is more concerned about the possibility of neurologic involvement. Sturge-Weber syndrome (SWS) is characterized by facial PWS with associated leptomeningeal angiomatosis, which may result in seizure and/or neurologic deficits. Glaucoma and other ophthalmic complications are frequent. The PWS of SWS must be located in the dermatome served by the ophthalmic (V1) branch of the trigeminal nerve.[6] SWS is most frequently associated with PWS involving both upper and lower eyelids, although there may be involvement of the other branches of the trigeminal nerve as well as PWS of other body areas. Facial PWS alone is insufficient for diagnosis. There is only an 8% association of ocular or central nervous system (CNS) involvement in infants with capillary malformation in the trigeminal nerve dermatomes. The risk of SWS is higher (19%) with more extensive unilateral PWS (involving V1, V2, and V3) (Fig 1) or with bilateral trigeminal nerve PWS (24%).[7] Some persons with SWS will have associated vascular malformations in other body regions that may be accompanied by overgrowth (Fig 2).

The extent of the cutaneous, ocular, and CNS involvement in SWS is quite variable. Neurologic outcomes range from normal intellect and no seizures to intractable seizures with retardation. The neurologic involvement is due to leptomeningeal angiomata, which are theorized to result from the first-trimester embryologic failure of the primitive cerebral venous plexus to regress. The lesion generally occurs ipsilateral to the facial PWS in the occipitoparietal region. Bilateral leptomeningeal angiomata are seen in 20%. The lesions are generally nonprogressive, but the associated alteration to blood flow results in anoxic injury to the underlying cerebral cortex[8] with cortical atrophy, sclerosis, and calcification. This damage leads to seizures that, in turn, cause further damage.

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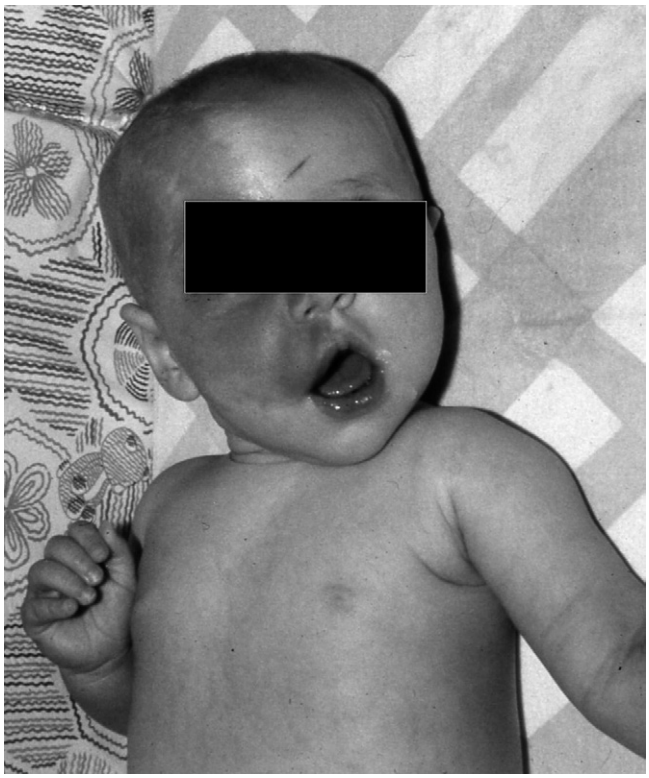

Figure 1 Infant with facial PWS in the facial nerve dermatome placing him at risk for SWS.

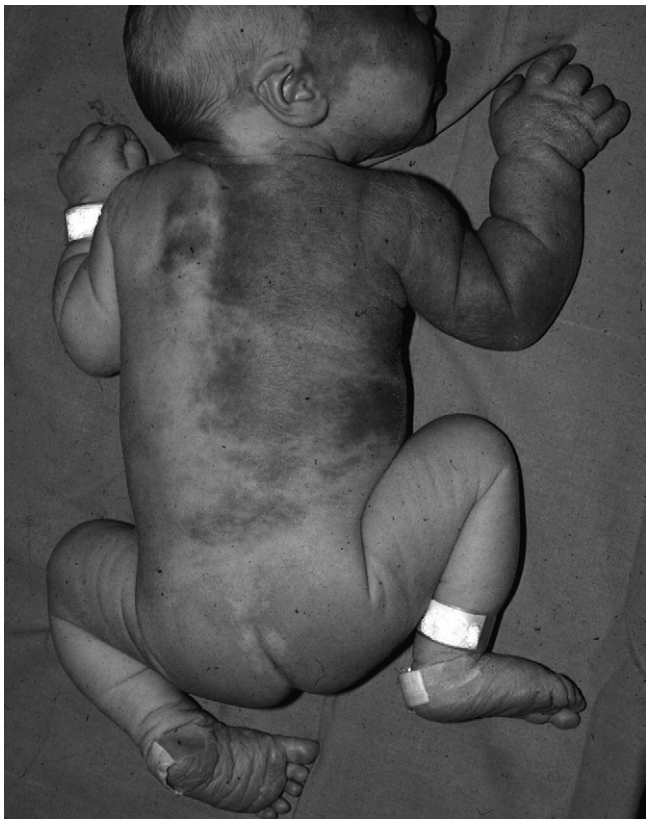

Figure 2 Infant with SWS and more extensive PWS and hemihypertrophy of the affected arm.

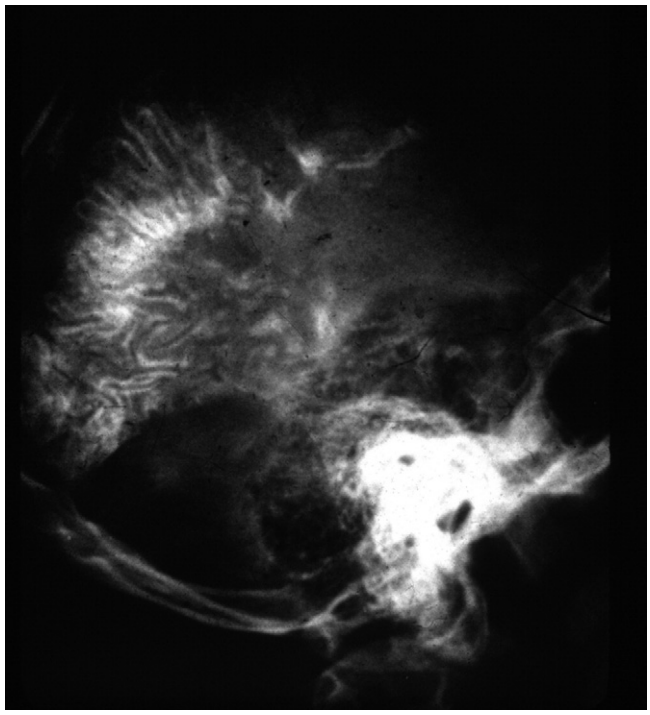

Figure 3 Skull xray in SWS showing the classic parallel curvilinear calcification.

Seizures are the most common neurologic presentation in SWS occurring in 55% to 90%. In 75% of those with seizures, onset is prior to 1 year of age.[9] Bilateral leptomeningeal involvement is associated with a higher risk of mental retardation and earlier seizure onset with more difficult seizure control.[10] Initial seizure type is usually focal motor with progression to generalized. With advancing age, seizures often occur more frequently and are harder to control. Interictal electroencephalogram (EEG) reveals decreased amplitude over the affected hemisphere and the degree of asymmetry shown on quantitative EEG has been correlated with the degree of brain involvement as evinced on cranial magnetic resonance imaging (MRI) as well as by clinical course.[11]

Management of the newborn with a facial PWS begins with a thorough physical examination to document the involved dermatome of the lesion as well as any other PWS. A visual inspection for any associated bony or soft-tissue hypertrophy should also occur. Ophthalmic consultation is essential in the newborn period to assess for glaucoma or buphthalmos caused by underlying choroidal angioma. Glaucoma is common (60%)[12] and is usually ipsilateral to the PWS but may be contralateral.[9] Other ophthalmic complications include angiomas of the conjunctivae or cornea, optic atrophy, retinal detachment, strabismus, hemianopia, or cortical blindness.[13] If the initial eye examination is normal, close monitoring is recommended with examinations every 3 months for the first 2 years of life and then annually.[9]

It is difficult to distinguish those patients with trigeminal PWS who will subsequently develop SWS from those who will have no intracranial involvement. Routine cranial imaging in the absence of neurologic or ophthalmic signs is not

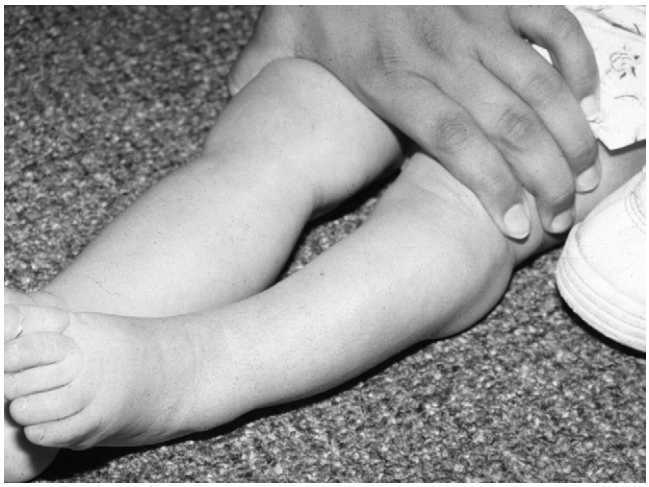

Figure 4 Toddler with pseudoarthrosis of the left tibia and fibula. This child was diagnosed clinically with NF1 after ten faint truncal CLS were visualized using Wood lamp.

currently recommended because a normal scan may give false reassurance that the facial PWS is an isolated anomaly when, in fact, the intracranial findings of may develop later.[14] Imaging should be prompted by neurologic concern such as seizure, developmental delay, or ocular findings (proptosis and glaucoma). The railroad track sign of parallel linear calcifications is not usually congenital but appears at about 2 years of age (Fig 3).[9] Gadolinium-enhanced T1-weighted spin-echo MRI will show the extent of the vascular malformation, but the size of the lesion is not necessarily correlated with neurologic outcome.[15] Advancements in imaging techniques are being studied for their usefulness in the early or presymptomatic identification of intracranial involvement in SWS and may alter the recommended timing of such studies if preventive interventions can ensue. Single-photon emission computed tomography and blood-oxygen level–dependent magnetic resonance venography may detect vascular involvement before there are signs of damage.[14] Positron-emission tomography and functional imaging techniques aid in prognostication and in identifying lesions that may be amenable to surgical resection.[16]

EEG in the child with facial PWS is typically not recommended unless there is clinical seizure activity or other indicator of intracranial involvement. Seizures usually respond initially to anticonvulsants but, with disease progression, may become refractory with a high incidence of status epilepticus. Surgery to remove the involved region or a complete hemispherectomy may need to be considered.[17,18] Researchers are investigating the use of quantitative EEG technology for earlier and less invasive identification of those children who are at risk for neurologic involvement and seizures, and their work may aid in developing preventive interventions such as more precise surgical resection.[11] Good seizure control has been shown to improve developmental outcome.[15]

The cosmetic aspects of PWS should be promptly addressed with families. With age, the PWS often darkens and can become nodular.[19] However, there has been success at fading the lesions using pulsed dye laser treatments. Complete clearance of the lesion has been achieved in approximately 22% of cases, particularly those of smaller initial size.[20] Results are best when started before age 7 years,[21] and treatment is safe in the first few weeks of life.[22]

Children with suspicious facial PWS should have close monitoring of their cognitive development and periodic neurologic assessments. Early developmental milestones are generally met on time in SWS; however, approximately 50% will have developmental delay or mental retardation[12] because of progression of the CNS disease. Refractory seizures are associated with poor developmental outcome in SWS with seizure intensity rather than age of onset being the important predictor.[17] Adult IQ is normal in 30% of those with seizures and in 100% of those without seizures.[10,12] The CNS dysfunction resulting from seizures and episodic hypoperfusion as well as the cosmetic impact of the facial PWS leads to frequent behavioral and emotional problems.[12,15] There is a high incidence of attention deficit-hyperactivity disorder. At least 30% of individuals with SWS have hemiplegia, with a larger percentage affected if brief transient episodes are included.[9] Frequent headaches are likely a reflection of variations in blood flow because of the underlying capillary malformation and may be temporally related to seizure activity. Antihrombotic agents may diminish damage caused by thrombotic events precipitated by sluggish blood flow.[15]

Neurofibromatosis 1 and Neurofibromatosis 2

Another dermatologic finding which signals possible neurologic involvement is multiple café au lait spots (CLSs). Neurofibromatosis type 1 (NF1) is the diagnosis most ofter considered in this scenario, although CLSs are not pathognomonic of NF1. The CLSs in NF1 are of uniform color with smooth borders and are usually easy to detect (Fig 4). A Wood lamp helps visualize faint spots. CLS may or may not be present at birth. They appear primarily on the trunk, buttocks, and extremities and less often on the face. It is unusual for an individual with more than 6 CLSs to be unaffected with NF1.[23] Families should be reassured that CLSs are themselves completely benign and that the number of spots, beyond the first six, that develop is not specifically related to the severity of NF1. The diagnosis of NF1 is a clinical one based on diagnostic criteria (Figs 5 and 6; Table 1).[24] The clinical features and associated complication have recently been well described in this journal[25] and thus will not be detailed again in this review.

NF1 is an evolving disease with manifestations occurring over time as outlined in Table 2.[26] Figures 4-6 illustrate some of the associated findings in affected persons of differing ages. Although less than 50% of sporadic NF1 cases meet diagnostic criteria by 1 year of age, 97% do so by 8 years and 100% by 20 years of age.[26] Thus, determining if a child with CLSs has NF1 requires patience and understanding on the part of the parents. At the first visit, a detailed family history is obtained assessing for family members with CLSs or other man-

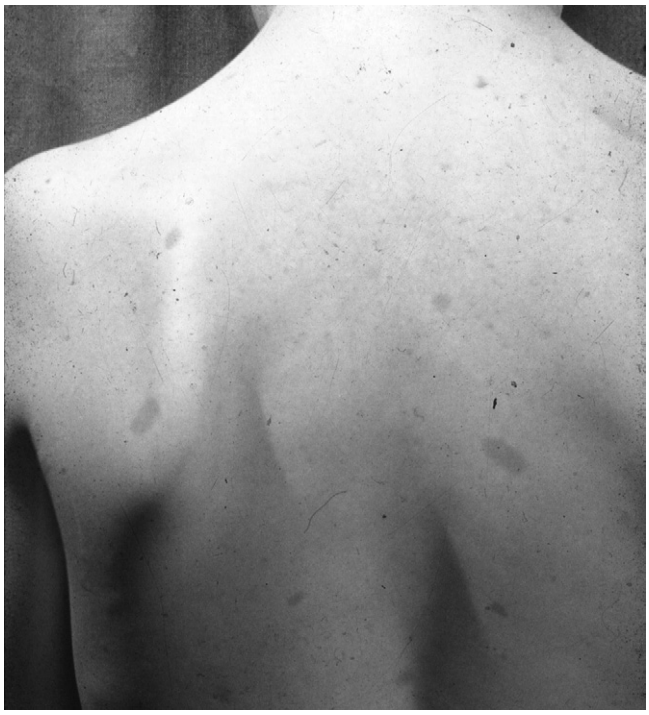

Figure 5 Teen with NF1 showing multiple CLS and a few cutaneous neurofibromas (lower left) and scoliosis.

ifestations of the various disorders potentially associated with CLSs. The child as well as both parents are examined and referred for ophthalmic examination to determine if any of them meets diagnostic criteria. In the absence of a positive family history, children with multiple CLSs but no other features cannot yet be definitely diagnosed but can be given a provisional diagnosis of NF1 and monitored. My personal approach is to examine young children with CLSs 1 to 2 times per year in the first 3 years and then annually, spacing the visits between routine primary care visits. Ophthalmic examinations are recommended annually until age 7 years in children with known or suspected NF1 and should include visual acuity, visual fields, color vision, fundoscopic examination (direct and indirect), and slit-lamp examination.[27] After age 7 years, those with known NF1 and without optic pathway tumor may have less frequent eye examinations, although recent study found that optic gliomas may still arise at an older age[28,29] requiring continued vigilance to the signs of tumor. Periodic ophthalmic examination to assess for Lisch nodules is helpful diagnostically in those who do not meet clinical diagnostic criteria because these lesions are eventually found in virtually all affected persons.

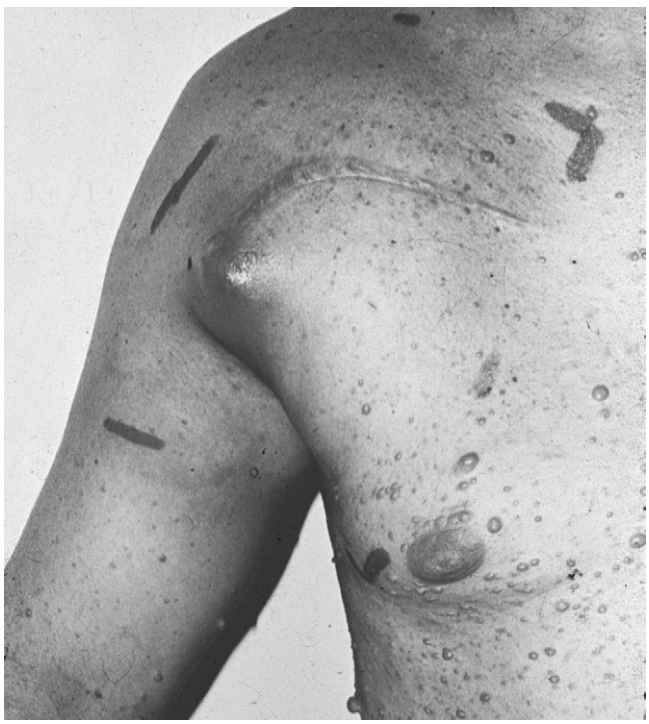

Figure 6 Adult with NF1 who has developed hundreds of cutaneous neurofibromas.

Table 1 Diagnostic Criteria for NF1 and Clinical Diagnosis of NF1 (2 of the 6 Following Criteria Are Met)

Skin
1. ≥6 CLSs: at least 1.5 cm in diameter (postpubertal) or 0.5 cm in diameter (prepubertal)
2. ≥2 neurofibroma of any type or 1 plexiform neurofibroma
3. Intertriginous freckling: axilla, inguinal, neck, breast
Ophthalmic
4. ≥2 Lisch nodules or 1 optic glioma
Skeletal
5. Distinctive osseous lesion: long bone bowing, pseudoarthrosis, or sphenoid dysplasia
Family history
6. Known or strongly suspected affected first degree relative with NF1

Adapted from the NIH Consensus Development Conference, 1999.[24]

Cranial imaging in the absence of CNS signs or visual disturbance is discouraged in NF1 because such imaging may reveal asymptomatic lesions of little or no clinical significance that create anxiety once identified. Significant, albeit infrequent, intracranial lesions of NF1 include brain tumors (predominantly nonprogressive grade I astrocytomas), aque-

Table 2 Age-Dependent Expression of NF1 Features

≥6 CLS	99% by 1 year
	1st development of CLS >4 years rare
Intertriginous freckling	90% by 7 years
	1st appearance >7 years rare
≥2 Lisch nodules	70% by 10 years
	99 to 100% by 20 years
Optic glioma (symptomatic)	1% by 1 year; 4% by 3 years
≥2 neurofibromas of any type or 1 plexiform NF	48% by 10 years; 84% by 20 years
Characteristic osseus lesion	14% overall, most appear by 1 year

Adapted from Debella, et al, 2003.[26]

Table 3 Clinical Diagnostic Criteria for NF2

Confirmed (definite) NF2
Bilateral vestibular schwannomas
or
Family history of NF2 (first-degree family relative) and
Unilateral VS <30 years of age or
Any 2 of the following: meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
Presumptive or probable NF2
Unilateral VS <30 years of age and
At least 1 of the following: meningioma, glioma, schwannoma, or juvenile posterior subcapsular letnicular opacities/juvenile cortical cataract
or
Multiple meningiomas (2 or more) and
Unilateral VS <30 years of age OR
One of the following: glioma, schwannoma, or juvenile posterior subcapsular letnicular opacities/juvenile cortical cataract

Adapted from Guttman, et al., 1997.[41]

ductal stenosis because of proliferation of subependymal glial cells around the aqueduct, intraspinal tumors, spinal meningoceles, sensorimotor peripheral neuropathy, and cerebral vascular disease leading to stroke.[30,31] Suspicious signs or symptoms of such processes warrant further investigation and treatment. Precocious puberty may be a sign of optic pathway glioma involving the chiasm[32] and should prompt cranial imaging. Seizures are uncommon in NF1, occurring in 3% to 5%. Brain tumor is the most common cause of seizure, although cortical malformation has also been reported.[33]

Children with a known or provisional NF1 diagnosis should have careful monitoring of their neurodevelopment. Learning disabilities occur in up to 60%.[34] No clear profile on testing has been seen despite many attempts to characterize the learning disabilities in NF1.[34,35] Mental retardation occurs in 3% to 8%[30] and, when accompanied by dysmorphic features, may signal an underlying large NF1 gene deletion potentially disrupting contiguous genes.[36,37] Autism does not occur more frequently than in the general population.[38] Psychiatric dysfunction is noted in 33%, with dysthymia most prevalent (21%). There is an increased rate of depression, anxiety, and personality disorders.[31] The recent study by Page and coworkers[39] documents the significant impact of the cosmetic and medical aspects of this disease on the quality of life.

Because CLSs are not pathognomonic of NF1, a differential diagnosis must be kept in mind for those with CLS who do not meet clinical criteria for NF1. Several syndromes may present with both CLS and neurologic manifestations, but they can usually be easily differentiated from NF1 based on the complete clinical picture and family history. For example, CLSs are seen in 33% to 50% of those with neurofibromatosis type 2 (NF2) but rarely as many as six,[40] and intertriginous freckling does not occur. NF2-associated skin tumors can overlap in appearance with those in NF1 including NF2 plaques (discreet, slightly raised, well-circumscribed patches of roughened skin that are usually <2 cm in diameter and may be hyperpigmented and/or hairy[30]), nodular schwannomas (mobile, subcutaneous, well-circumscribed lesions that have similar appearance to NF1 lesions but are schwannomas rather than neurofibromas by pathology[40]), and dermal neurofibromas (intradermal papillary violoceous skin tumors similar to those in NF1 but occurring in far fewer numbers[30]). Diagnostic criteria for NF2 are useful in differentiating it from NF1 (Table 3).[41] These and previously proposed criteria have been critically evaluated, and none are able to detect all cases of NF2,[42] making it crucial for the practitioner to be aware of the various presentations and to maintain an appropriate level of suspicion for nonclassic cases. Most persons with NF2 come to attention because of symptoms of bilateral vestibular schwannoma such as hearing loss, tinnitus, vertigo, or balance issues, which are uncommon complaints in NF1. Mild to moderate progressive hearing loss, either unilateral or bilateral, is the most common presenting symptom, being noted in 44%. Focal weakness, likely caused by spinal tumor or neuropathy, is the initial finding in 12%. Twenty percent to 30% of those with NF2 present with intracranial meningioma, spinal tumor, or cutaneous tumor[43] and less frequently with seizures or vision loss.[44] Up to 31% will have multiple or nonspecific complaints at presentation.[40]

The pediatric presentation of NF2 deserves special mention as this disorder often goes unrecognized in childhood, particularly in the absence of a family history (which is expected in half of all cases). Evans and coworkers[43] discovered that 18% of patients in their NF2 database presented between birth and 15 years of age. In contrast to adults, children are less apt to present with hearing loss or tinnitus.[44] Meningioma was the presenting sign in 31%, spinal tumor in 11%, and cutaneous tumor in 8%. Of interest is that 10% to 18% of children with no suspicious family history who presented with what appeared to be isolated meningioma or schwannoma later developed criteria for diagnosis of NF2, resulting in recommendation that the diagnosis of NF2 be considered for all children presenting with such tumors. Children presenting with cutaneous neurofibroma or cutaneous schwannoma with fewer than 6 CLSs should also be monitored for NF2.[43] Evans and coworkers[45] published a consensus statement reviewing the recommended management of NF2 including surveillance imaging for CNS and spinal tumors and ophthalmic and audiologic monitoring. They documented that individuals with NF2 have improved outcomes when managed in a center specializing in treatment of NF2 and that a philosophy of "minimal interference" results in the best overall functional and cosmetic outcome.

Bannayan-Riley-Ruvalcaba Syndrome

CLSs may be found in 2 overgrowth syndromes of particular importance to the neurologist: Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Proteus syndrome (PS). BRRS is associated with generalized somatic overgrowth of prenatal onset.

Table 4 Revised Diagnostic Criteria for Proteus Syndrome

General criteria
Must have all of the following:
√ Mosaic distribution of lesions
√ Sporadic occurrence
√ Progressive course
Specific criteria
Must have 1 from category A, or 2 from category B, or 3 from category C:
√ Category A: cerebriform connective tissue nevus
√ Category B:
1. Linear epidermal nevus
2. Asymmetric, disproportionate overgrowth involving 1 or more of:
a. limbs, arms/legs, hands/feet/digits, or extremities
b. Hyperostoses of the skull
c. External auditory meatus
d. Megaspondylodysplasia
e. Viscera: spleen/thymus
3. Specific tumor before 2nd decade (1 of the following):
a. Ovarian cystadenoma
b. Parotid monomorphic adenoma
√ Category C:
1. Dysregulated adipose tissue (one of the following):
a. Lipomas
b. Regional absence of fat
2. Vascular malformation (one or more of the following):
a. Capillary malformation
b. Venous malformation
c. Lymphatic malformation
3. Lung cysts
4. Facial phenotype (all of the following)
a. Dolichocephaly
b. Long face
c. Downslanting palpebral fissures and/or minor ptosis
d. Low nasal bridge
e. Wide or anteverted nares
f. Open mouth at rest

Adapted from Turner, et al.[55]

Birth weight may be greater than 4 kg, and birth length is greater than the 97th percentile. Growth rate decelerates postnatally with body weight and height in most older children and adults being within the normal range.[46] All cases have macrocephaly which is usually congenital and is caused by a benign increase in brain size[47] with normal ventricular size (megalencephaly).[46] Dysmorphic features may be present and include downslanting palpebral fissures, depressed nasal bridge, long philtrum with thin upper vermillion border, wide mouth, high-arched palate, and micrognathia.[48,49] Joint laxity, pectus excavatum, and scoliosis are common.[46] CLSs occur in some, but the characteristic skin finding is pigmented macules of the glans penis and penile shaft ("speckled penis"), which may be present at birth or develop in childhood or adolescence in up to 90% of affected males. The penile freckles are often subtle and thus overlooked unless specifically assessed.[46,49] Freckling in NF1 may occur in the inguinal crease but does not extend to the penis.

Neurologic sequelae of BRRS occur in up to 70%[50] of diagnosed cases. A characteristic myopathy of the proximal muscles has been described with fiber size variation and neutral lipid droplets in type I fibers on muscle biopsy. The myoliposis is not seen in all cases and may be age dependent.[48] It may be focal such that several biopsies may be needed to show this finding. Speech and motor delays are seen in 50% but often improve with age such that adults have normal IQ but may have residual motor dysfunction. Mental retardation does occur with some families showing more cognitive impairment in the children than in the parent.[49] Seizures occur in 25%.[46] BRRS is associated with lipomas, hemangiomas, and angiolipomas that may be cutaneous, intracranial, or intraosseous and are usually slow growing and easily resectable but may be aggressive and deforming.[51] Hamartomatous polyps may occur throughout the gastrointestinal system, particularly in the colon and rectum and lead to watery diarrhea, abdominal pain, and rectal bleeding.[48] Management of those with BRRS is largely symptomatic, although carnitine has been shown to improve the myopathy.[52,53] BRRS overlaps phenotypically and molecularly with Cowden syndrome, a familial cancer syndrome. Thus, affected individuals may be at an increased risk for cancers of the breast, thyroid, and endometrium indicating a need for awareness and appropriate surveillance.[54]

PS

PS is a rare phakomatosis that is often overdiagnosed so that strict clinical diagnostic criteria have been proposed (Table 4).[55] Application of these criteria to published PS cases resulted in only 47.3% being confirmed as PS, indicating that a variety of overgrowth conditions and other phakomatoses have been mislabeled as PS. The overgrowth in PS is distinguished from other overgrowth conditions in that it is asymmetric, distorting, and relentless and occurs at a rate faster than the growth rate of the rest of the body. Dramatic enlargements of a limb or a digit can be seen and impairs function as well as being of significant cosmetic impact. Abnormalities are usually not apparent at the time of birth, although there have been PS cases with congenital overgrowth. Areas of deficient growth can occur in PS, which is not seen in classic overgrowth syndromes. For example, bony overgrowth in PS may be accompanied by lipohypoplasia and dermal hypoplasia, whereas other overgrowth syndromes are accompanied by ballooned soft tissues.[56] Round exostoses of the skull commonly occur in the frontotemporal or parietooccipital region.[57] The cutaneous manifestations of PS are the most distinctive features and are congenital or early in onset. They include linear verrucous epidermal nevi, connective tissue nevi, and cutaneous vascular malformation. The cerebriform connective tissue nevus is the most characteristic finding in PS and is commonly located on the sole of the foot as thickening and furrowing of the skin and subcutaneous tissue that resembles the surface of the brain, hence the term "cerebriform hyperplasia." They can also occur on the palms, trunk, perinasal area, or near the canthus of the eye. They are well-demarcated progressive plaques of confluent papules and

Table 5 Genetic Aspects

Neurofibromatosis 1*
Autosomal dominant: 50% inherited, 50% de novo
Neurofibromin gene at 17q11.2
With multistep mutation analysis:
>95% of those meeting clinical criteria have mutation
Neurofibromatosis 2*
Autosomal dominant: 50% inherited, 50% de novo
Merlin gene at 22q12.2
With multistep mutation analysis
>90% of those with inherited NF2 have mutation
72% of those with de novo NF2 have mutation
25 to 30% of de novo NF2 cases are mosaic and may not be detected
BRRS*
Autosomal dominant
PTEN gene at 10q23.31
With sequence analysis
Mutation in 60%
With deletion analysis
An additional 11% have large deletion
SWS
Sporadic
Unknown, possible gene(s) involved in neurovascular development
PS
Sporadic
Unknown, presumed tumor suppressor gene(s) or growth regulatory gene(s)

*GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1993 to 2007. Available at http://www.genetests.org. Accessed May 13, 2007.

nodules that are pink or flesh colored. Those on the sole tend to begin on the ball of the foot near the arch and then extend to cover the entire surface. Management of cerebriform connective tissue nevus has proven quite difficult with limited success of surgical interventions, particularly for those on the sole because of postoperative keloid formation, pain, and infection. The epidermal nevi are well-circumscribed hyperkeratotic papules of tan or brown color occurring in linear streaks along the lines of Blaschko. The dermatologic features tend to be progressive, although in rare cases they regress. A few small CLSs or hypopigmented patches may be seen.[57,58] The number of skin lesions has been correlated with the number of extracutaneous manifestations, indicating that those with more skin involvement should be investigated for internal involvement.[58] Vascular malformations include capillary PWS, venous anomalies, and vascular tumors that usually involve the trunk or limbs.[58,59] The vascular tumors follow a different clinical course than typical hemangiomas in that they continue to grow slowly until 12 to 14 years of age rather than regressing, and they have a higher rate of thrombosis, thrombocytopenia, or phlebitis.[59] Tumors occur frequently, particularly in the thoracic, abdominal, and gluteal areas and include lipomas, lymphohemangiomas, and lipohemangiomas.[57] The lipomas are soft and skin colored with poorly defined borders that vary in size from small nodules to large invasive lesions. They are generally benign but may act aggressively and are frequently disfiguring.

Neurologic involvement in PS occurs in 40%[55] of cases and includes moderate mental retardation in approximately 20%[50] and seizures in 12.7%,[57] both of which may signal associated hemimegalencephaly. Children with PS who have CNS malformation, seizures, and mental retardation are more apt to display the facial phenotype[59] (Table 4). Other neurologic findings include hydrocephaly, thickened leptomeninges, dural ectasia, polymicrogyria, periventricular heterotopias, cystic lesions, subependymal nodules, and calcifications. There is a small increased risk of intracranial tumors including meningiomas and astrocytomas. Vertebral anomalies and spinal canal lipomas may lead to spinal stenosis and associated peripheral neurologic deficits. Clinical management of the host of possible complications that may arise in nearly any system of the body requires a multidisciplinary team. Cranial MRI should be performed at diagnosis and repeated as indicated clinically. Periodic ophthalmologic examinations are recommended because of the 42% association of structural and functional anomalies of the eyes. Pulmonary embolism is a major contributing factor to early mortality in PS so that clinicians and PS individuals need to be alert to the symptoms. Periodic testicular or ovarian ultrasounds are recommended because of the increased risk of reproductive tumors.[55] As with other phakomatoses, the possibility of depression and self-esteem issues should be anticipated and appropriate counseling and therapies recommended.

Genetic Aspects

The genetics of the phakomatoses are varied (Table 5); however, they share in common the feature of mosaicism. SWS has no known underlying gene defect, although genes involved in regulation of neurovascular development are likely candidates and are being pursued.[60] SWS is sporadic and thus not expected to recur in the children or siblings of those affected. The capillary malformation and leptomeningeal angioma of SWS occur in a limited region, indicating the likelihood of a mosaic underlying genetic abnormality. Studies have found a variety of chromosomal abnormalities in the PWS skin that are not found in unaffected skin[61] consistent with the mosaicism theory, but such abnormalities are not found in all PWS. Until the gene or genes and any epigenetic or environmental factors involved in the pathogenesis of SWS are identified, the mosaicism hypothesis remains unproved. Similarly, PS is a sporadic disorder with no clear causative gene mutation. Mutations in the tumor suppressor gene PTEN have been reported in PS,[62,63] but others have proven that patients who meet strict diagnostic criteria for PS do not have PTEN mutation.[55,64] The patchy nature of PS manifestations is consistent with a probable underlying mosaic state caused by a postzygotic gene mutation as is the fact that the PS is not an inherited disorder. The responsible gene will likely be a tumor suppressor gene or other gene involved in regulation of cell growth.

NF1, NF2, and BRRS are each autosomal dominant disorders associated with gene mutations in a tumor suppressor gene.

Again, the patchy nature of the disease manifestation indicates a mosaic state, but each of these disorders is heritable indicating that the gene mutation is not simply caused by a postzygotic mutation. The responsible mutation is present at the time of conception, either as a gene inherited from an affected parent or as a new mutation. Tumor suppressor function is still intact because of the second, unaffected, copy of the gene. It is proposed that there is loss of this functioning gene copy at the individual cellular level over time leading to uncontrolled growth of these cells. This process is known as loss of heterozygosity. Because loss of heterozygosity does not occur in every cell, there is mosaicism at the cellular level, which explains the patchy nature and age-dependent appearance of the disease manifestations as well as the wide range of both intra- and interfamilial variability noted in these phakomatoses.

Genetic counseling is a critical aspect of management of the phakomatoses. In SWS and PS, the parents can be reassured that recurrence in another child is unlikely. The affected child can be similarly counseled about his/her own children when he/she reaches an appropriate age. Advances in our molecular understanding of these 2 disorders may allow for more specific risk analysis in the future. For each of the phakomatoses, a thorough family history must be documented and both parents properly examined to determine if the disease is occurring as a new mutation or has been inherited from a potentially undiagnosed parent. In NF1, NF2, and BRRS, the absence of an affected parent indicates a low, but not zero, recurrence risk because of the possibility of germline mosaicism in which a parent has mutation in the gonadal tissue only and thus no clinical manifestations. In such cases, there is the possibility of having more than 1 affected child, but there is currently no method to assess for gonadal mosaicism, and families are given an approximate recurrence risk of 1%. When a parent has a known diagnosis of an autosomal dominant phakomatosis, the recurrence rate is 50% for each child, but the clinical outcome (mild to severe) cannot be predicted based on clinical features in the affected family members or by our current molecular technology. One exception is NF2 in which, despite significant interfamilial variation, the age of onset and clinical course within a family tends to be similar. Genetic testing can be used for prenatal or preconception diagnosis of these disorders, and affected adults should be asked for their feelings about having an affected child. Testing is best done with the help of a geneticist or genetic counselor to ensure that full informed consent is obtained and that the appropriate testing protocol is followed.

Genetic testing in children carries a host of ethical concerns[65] and should not be done lightly in the asymptomatic or presymptomatic child. Gene testing of a child who is the index case may be undertaken if either of the parents is considering another child and wishes to consider preconception, preimplantation, or prenatal testing. Gene testing is not warranted for children who have insufficient findings for clinical diagnosis of NF1 because they can be monitored clinically until their status becomes clear. Children with manifestations suspicious of a diagnosis of NF2 (eg, meningioma or schwannoma) in the absence of a family history should be offered gene testing along with tumor analysis in an attempt to clarify if they are at risk of development of other tumors.[43] Children of a parent affected with NF2 should be offered gene testing at about 10 years of age to determine if they are in need of starting a program of CNS and spinal tumor surveillance. Earlier testing can be done if the family history suggests early onset of tumor development. Before gene testing, these children should have undergone annual ophthalmologic and audiologic surveillance.[45]

PTEN mutation testing should be part of the diagnostic investigation of both adults and children with clinical features of BRRS. Only 57% to 60%[66,67] will have an identifiable PTEN mutation indicating that there may be other causative genes, perhaps genes functionally associated with PTEN. Some families have both individuals affected with BRRS and individuals with Cowden syndrome, indicating that gene testing should be offered to family members of persons diagnosed with either of these PTEN-associated conditions.[49,68] Butler and coworkers[69] suggest that PTEN testing should be considered in the diagnostic investigation of extremely macrocephalic (>4 standard deviation above the mean) children with autism given their finding of PTEN mutation in 17% of such children who had few or no other BRRS features.

It is hoped that advances in our understanding of the molecular underpinnings of these phakomatoses will bring about specific therapies targeted at the gene level, which will ameliorate or prevent the associated complications. When such therapies are available, it will be important to gene test asymptomatic at-risk children as well as children with a provisional diagnosis to offer them effective preventive measures.

In summary, the skin is an important indicator of potential underlying CNS disorder. The neurologist faced with a child with undiagnosed mental retardation, developmental delay, seizures, or autism should perform a thorough skin examination with the help of a Wood lamp. Conversely, when pigmentary lesions are identified in a child, the clinician should be vigilant to possible neurologic sequelae. Clinical criteria are useful for diagnosis of the phakomatoses and gene testing is a helpful adjunct in certain scenarios. The phakomatoses have a wide range of outcomes both within and between families, and ongoing counseling is needed to empower families to best manage these diseases.

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